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THE NORMAL GASTRIC SECRETION.

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(Read April 14, 1916.)

The human gastric secretion has been the subject of persistent study ever since it was realized that there was apparently secreted a free mineral acid in the stomach. Not only has this fact, the presence of a true acid secretion, given rise to endless discussion, but the mechanism of gastric digestion has been attacked from every angle. The x-ray and especially the fluoroscope has thrown much light on gastric movements but has left us hopelessly in the dark as to the intimate chemistry and the respective physico-chemical changes which occur while the kaleidoscopic changes in form are recorded. It has until very recently been practically impossible to investigate either normal or pathological digestion satisfactorily in man. The fundamental principles were laid down by the painstaking work on fistulas on animals by the Pavlov school and a host of investigators who recorded many observations in man by means of the old stomach tube. With the exception of a few fistula cases such as the historic instance of Alexis St. Martin and the occasional case of gastric fistula consequent to an acquired stenosis of the esophagus there are no coordinated observations on normal digestion in man. This was owing to the lack of a method by which it was possible to follow every phase of gastric digestion. In spite of the lack of a method, the use of the bulky and wholly undesirable stomach tube was followed and many observations were made.

In the fall of 1913, while studying the work of Hayen, I endeavored to find a tube which could be introduced into the stomach and left in place. The original tube was a modification of the Ein-horn tube, but it was neither sufficiently heavy nor of sufficient calibre for this purpose. I then devised a special tip olivary in type and of such a form as to be easily swallowed and of sufficient weight to seek the bottom of the stomach, or the most dependant portion of

the greater curvature of the stomach by gravity. A number of tips were made, but finally one was found which was the most satisfactory—and it was slotted in such a way that the diameter of the slots represented the maximum bore of the rubber tubing. This in turn was glass molded in order that it gave rise to no irritation while in situ. This tube was swallowed in the natural way: it gives rise to practically no irritation and I was able to satisfy myself by radioscopic examination that it reaches the lower part of the stomach. Another important feature was the fact that this tube could be left in place for hours with practically no discomfort and that it constituted practically a "via ouvert" or a direct communication to the stomach at all times so that the progress of digestion could be accurately followed and the examination of the material removed faithfully recorded. For the first time it was possible to follow every step in the chemical evolution of digestion and at the Jefferson Medical College, under the supervision of Dr. Hawk and with the collaboration of Drs. Bergeim, Fowler, Spencer, Clarke and others, we began an extensive survey of normal and pathological digestion.

Before discussing the important findings regarding gastric digestion, the first salient feature which became apparent was the impossibility of interpreting the findings of a single examination of the stomach as determined by the old method. In a communication to the *Journal of the American Medical Association*, Vol. LXIV., pp. 567-573—I made the following statement which has been since confirmed by other workers (Carroll, Pollock, Talbot):

1. It is impossible to interpret the figures obtained by the examination of the test meal removed in one hour time by the usual technic.

2. The one hour period represents but one phase in the constantly changing cycle of gastric digestion.

3. It is absolutely impossible to judge from the old method what has preceded or what will follow this point.

We were able to show for instance that normal figures at the one hour point may be preceded or followed by entirely different phenomena in the brief course of 10 or 15 minutes and that for an accurate analysis of the phenomena, it is essential that we make an examination at every interval during digestion. This method of

examination, I have called the "fractional examination or determination of gastric digestion," because it consists in removing at intervals a fractional portion of the actively changing gastric contents for examination. From the material which is removed by aspiration, by newer methods a complete chemical, bacteriological and cytological examination may be made and curves constructed representing the progress of gastric digestion.

By means of this tube, the first important observation which we made was the nature of the material found in the empty stomach. It has been generally considered that this material should not exceed 20 c.c. in health. We found in a study of over 100 normal medical students, that the quantity of material in the empty stomach practically always exceeded this point and in the above series, the average was 52.14 c.c., more than twice the quantity formerly considered normal. We found furthermore that this material was in most instances a physiologically active secretion capable of inducing gastric digestion and giving as average figure for the above series a total acidity of 29.9 in terms of N/10 NaOH necessary to neutralize 100 c.c. of secretion (phenolphthalein) and 18.5 free acidity (Sahl method). Pepsin determination in 53 cases gave an average of (2.8). We were further able to demonstrate by means of a special method devised in our laboratories the presence of trypsin almost constantly in the residuum, which was shown to be inversely proportional to the free acidity.

In other words we found at whatever time we examined the stomach regardless of the presence or absence of food a physiologically active secretion in the stomach. If as was performed on several occasions, we removed the complete residuum and then without introducing food in the stomach examined the organ somewhat later, a physiologically active secretion could be removed even though in digestive power it was lower than the material seen during the digestive periods. In health therefore it is correct to assume that there is always a minimal secretion in the stomach which at regular intervals undergoes perturbations due to the influence of hunger, psychic influences of sight, taste, and smell of food, and finally the complex digestive cycle following the introduction of food into the stomach.

We found this "residuum" of the empty stomach one of the lightest fluids in the body with an average specific gravity of 1.0056 and an average cryoscopic index of —0.470 which when compared to the index of blood —.0560 seems to indicate a tendency for osmosis of material to take place from the blood into the lumen of the stomach. We found bile in almost one half the normal residua, and this phenomenon may be present or absent in the same individual without any subjective phenomena whatsoever.

We then made an investigation of many substances in the stomach of the normal healthy subject and used for that purpose water, meat extracts, tea, toast and since that time many of the various food-stuffs concerning which we shall have more to say in the future. In a convincing series of experiments on water it was immediately evident that water is a strong gastric stimulant and while it may be true that the bulk of the liquid leaves the stomach in the first twenty minutes along the "rinne" of the lesser curvature, we found that water either cold or warm is a strong gastric stimulant, yielding an acidity in certain instances of over 100 in less than twenty minutes. In the normal individual on many occasions water produced fully as great stimulation as an Ewald meal of toast and tea so that it became a serious question as to whether or not the stimulative effect of an Ewald meal was not due to its water content, but the dry toast induced a very definite characteristic secretion.

In our studies we were unable to demonstrate two essential points which have previously been considered as belonging to the phenomena of digestion. It was impossible to demonstrate any "latent period" for the human gastric glands, as Pavlov demonstrated in animals and secondly—it was impossible to demonstrate any glandular fatigue which Foster and Lambert attempted to point out. In the water series despite any possible dilution of the water introduced we obtained figures of from 50-120 (0.18-0.44 per cent. HCl) with an average of 77 (0.28 HCl) considerably over that ordinarily considered normal for man. It is probable that the juice secreted at the height of digestion is distinctly higher than that usually considered and the contention of Umber, Bickel, Sommerfeld, Hornberg and others that the gastric juice of man is very similar (0.4-0.5 per cent.) to the gastric juice of the cat and dog is true.

Some time ago Dr. Hawk and I published a paper on the direct evidence of the secretion of a gastric juice of constant acid concentration in the human subject. We have been criticized for considering the "digestive" plateau while food was in the stomach as evidence of this. On the contrary however—the evidence when there is no food in the stomach namely the "plateau" or "constant acid level" seen in certain cases after water introduction, presumably after all water has left the stomach or when the diluting action of water can be no longer felt and again the "constant acid secretion"—frequently seen after all food has left the stomach are the most powerful arguments for the secretion of a constant acid grade.

NORMAL SECRETORY CURVE.

For the investigation of gastric disturbances it becomes absolutely essential that we have a standard, any deviation from which constitutes a pathological finding. Such an arbitrary and concrete standard is obviously impossible because in every individual there is a characteristic functional output. It is possible to draw the limits of health for any group of individuals, but practically every group of bodily functions undergoes many variations owing to a multitude of variable factors in the course of the day. Under exact conditions the output is the same, but exact conditions are somewhat difficult to approximate. From a very large series of observations on normal healthy medical students, the following statements seem entirely justifiable:

- (a) Each individual has a characteristic gastric response.
- (b) Under identical conditions, physical and environmental, the type and character of the gastric response to a certain stimulus is essentially the same.
- (c) There are several varieties of normal secretory response, normal in that they are found in individuals absolutely free from gastrointestinal symptoms and to all intents and purposes enjoying perfect health.

We have tried various meals but for simplicity, availability and short gastric transit we have studied the Ewald meal 35 grams of toast and 240 c.c. of weak tea or water in an attempt to outline the normal gastric response.

We found that healthy medical students reacted to the Ewald meal in one of three ways:

1. The "isosecretory" type shows a steady rise, high point, in terms of tenth-normal sodium hydroxid, 60, usually sustained for from half an hour to an hour, and then a gradual decline with a total disappearance of the food residues in from two to two and one half hours.

The curve is usually steady and unbroken; its high point is usually rounded and not abrupt and is to be found in the neighborhood of one hour.

2. The "hypersecretory" type shows a rapid response to stimuli, often a marked change in the acidity even of the five-minute samples, rapid increase in acidity, high point from 70 to 100 or over, either sustained or abrupt, and a slow decline or none at all in the usual time. The food left the stomach in normal time from two to two and one half hours, but even after the passage of all food material there was often encountered an outpouring of pure gastric juice for half an hour, one hour, or even several hours. This finding, which was obtained in many cases, is so pronounced and distinct that we call it a "continued digestive secretion" in contradistinction to "hypersecretion" because it occurs in normal symptomless persons. This type we call the hypersecretory type because of the general tendency of the acidity to assume exaggerated proportions.

These represent but two of such curves in which the tendencies described were pronounced and the "continued" secretion was quite prominent. Several cases in which the acidity approached that seen in the isosecretory type likewise showed this phenomenon.

3. The third or "hyposecretory" type is similar to the first but there is usually a slower ascent, slower response to stimuli, and a high point from 40 to 50. Digestion is usually completed in two and one half hours. This is the type least frequently encountered.

A consideration of the curves from the examination of normal persons indicates that there is no normal curve which will hold for all cases.

A distinction should be made of terms "secretory" refers to the quantity of secretion, "acidity" to the quality or acid grade of the secretion. "Hypersecretion" means the individual who responds to

every stimulus with an abundant secretion, "hyperacidity" whose response although possibly not excessive is still of a high acid grade. However it is found that those individuals with excessive quantity compared to a normal mean usually show also hyperacid compared to a normal mean which one might call the "isoacid" figure.

In other words after studying the average collective response of all normal individuals it becomes apparent that while the motor function in perfect health varies within very narrow limits, the quantity and quality of the secretion has considerable variations. There is a group by no means small in which the secretion is very abundant, the acid figure high, and there is often present a post-digestive or continued secretion. These people always react in this way while there is a group diametrically opposed who show a rather tardive secretory response. Both are normal: both without symptoms: both must be considered in the analysis of any pathological case.

Careful study as far as I can ascertain seems to demonstrate that hypersecretory individuals give hypersecretory responses to all forms of gastric stimuli. Whether it be bread, bread and tea, meat, milk or a mixed meal—our "hypersecretory" students give always an hypersecretory response—and our hypersecretory normal type give as a rule with any form of stimulus a low or a so-called hyposecretory response. In the many experiments numbering several thousand we have been able to predict almost always the type of response which a certain individual would give after trying him out with a certain substance. Of course there are daily variations and extreme fatigue as well as gastric abuse will entirely change the gastric output as we have been able to demonstrate.

These findings are extremely important because they must make us cautious in drawing unwarranted diagnostic conclusions on the quantity and quality of the secretion. In over 40 per cent. of our cases, we found figures exceeding 60 total acidity and it is perfectly apparent that the diagnosis of pathological hyperacidity for figures exceeding 60 must be entirely rewritten when it is evident that this occurs at some phase in the digestive cycle of many normal individuals.

Over 30 per cent. of normal cases develop an acidity in excess of 70 or 0.25 per cent. HCl and the probabilities from our experi-

ments are that the perfectly pure secretion varies between 0.3-0.4 per cent. of HCl instead of the 0.2 per cent. of clinicians.

An extensive study was made of the psychic secretion and for this purpose healthy students were selected, the stomach evacuated and residuum removed before any food was taken, and the tube left *in situ*. They were then placed in front of a weighed steak, and the secretion from the sight and odor of food recorded by complete interval evacuations, this was followed by the chewing of the meat but no material could be swallowed, all meat being expectorated after a definite time interval of chewing. These experiments, the first ever performed on healthy non-traumatized human subjects, and as yet unpublished, are full of interesting data. In 33 separate observations on about 12 subjects, the following points were recorded:

(a) There is a definite psychic secretion varying in duration of from 60-80 minutes, perhaps longer if the psychic stimulus is continued.

(b) There is no latent period as Pavlov indicated.

(c) The amount of secretion in the series without atropine varied in 14 pure psychic cases from 105 c.c. to 274 c.c. with an average of 122 c.c. during the period. After the oral or hypodermic administration of atropine, which presumably cuts out the psychic responses, in 12 cases the quantity removed varied from 15.5 c.c. to 64 c.c., with an average of 37.6 c.c., a difference of 85.4 c.c. on the average or in other words of 69.2 per cent. (more than two thirds).

(d) There is evidence to believe that the chemical secretion is induced at a very early period, and probably occurs well in the first hour.

(e) In 12 out of 21 straight experiments without atropine the acidity exceeded a total acid of 70 varying from 74 to 114.5 T. A. 0.41 HCl with an average of 97.3 c.c. indicating in over one half the normal psychic responses give an acidity in excess of 70 while the average is equal to or above this point. This finding is supplemented by the fact that in 14 out of the 21 cases the free acid exceeded 50, the figure frequently given for normal total acidity. These findings in themselves throw an entirely different light on the

whole subject of pathological gastric chemistry. In only two instances out of 12 atropine experiments did the total acidity exceed 70 (16.6 per cent.) and they were 79.5 and 71.5 respectively, while in four of those cases (33 per cent.) the free acid exceeded 50. In other words, it was possible to demonstrate directly a definite reduction both in the quantity and in the acidity of the psychic secretion after the administration of atropine.

(f) On a pathological case (ulcer) we were able to demonstrate a marked increase in the quantity of the psychic secretion under the same circumstances as well as an increased velocity in the formation of the secretion.

While the psychic response may vary markedly under certain circumstances, the phase which we call chemical late in digestion and which we attribute to secretagogues, hormones, the formation and absorption of certain gastrins, is remarkably constant.

Normally the factor of safety is very great in the stomach, but any pronounced deviation from normal whether due to excessive ingestion of indigestible food, indulgence in alcoholic liquors or to marked fatigue of any kind is usually followed by recognizable gastric disturbances, among which are a tendency to excess of or persistent secretion and frequently minimal food retention due to disturbed motility.

A consideration of the foregoing facts enables us to construct a rational basis for the interpretation of pathological phenomena. In the first place it must be evident that normally the evacuation time is remarkably constant. Abnormally any variation can occur from a marked acceleration of the gastric contents seen in certain forms of achylia and in the accelerated peristalsis of certain forms of duodenal ulcer and duodenal irritation to the delayed evacuation only partial seen in certain forms of atony to the pronounced delays seen in the various forms of pyloric stenosis.

From a secretory standpoint, many things may occur. The evolution may be entirely abnormal. The development of the secretion may be accelerated or retarded, in reality delayed gastric digestion; or there may be at any phase in the gastric cycle the entrance of pronounced secretory perturbations as hypersecretion or the elimination or secretion of a juice of high acid grade. The

reverse, disturbances pointing to insufficient acidity and secretion are found.

While this is not the place to discuss the question of ulcer and cancer, the former has a constant tendency to induce gastric phenomena of the spastic type together with excessive secretion and increased acidity, while the presence of the latter has a definite downward tendency on the secretory causing either an inhibition or neutralization or late formation of the secretion due to a mucosal lesion. Every variety of change in the specimens can occur from positive disturbance in the quantity and quality of the secretion to the admixture of purely pathological exudates or transudates consisting of blood, pus, bacteria which are more or less characteristic of certain conditions as well as definite fermentative phenomena seen in certain forms of stasis. A recognition of the normal type and its thorough understanding is essential to the interpretation of the pathological responses which occur.